ELSEVIER

European Journal of Pharmacology 405 (2000) 351–363

ejp

www.elsevier.nl/locate/ejphar

Antidepressants: past, present and future

Jerzy Vetulani *, Irena Nalepa

Institute of Pharmacology PAN, Polish Academy of Sciences, Smetna 12, 31-343 Cracow, Poland

Accepted 28 June 2000

Abstract

Since the discovery of first antidepressants in mid-1950's, the field has been intensively studied. Several new classes of compounds emerged and several hypotheses on the mechanism of their action were proposed. The novel antidepressants are either selective and reversible monoamine oxidase inhibitors, (e.g., moclobemide), or selective serotonin reuptake inhibitors (e.g., citalopram or paroxetine), or serotonin and noradrenaline reuptake inhibitors (e.g., venlafaxine). Recently neuropeptides (e.g., thyrotropin-releasing hormone,TRH) or antagonists of neuropeptide receptors (e.g., tachykinin NK_1 receptor) undergo clinical tests. Several hypotheses proposed the predominant involvement of one or few neurotransmitter receptors in the mechanism of antidepressant action, but it is now assumed that several distinct receptor mechanisms' trigger different but converging intracellular signal cascades that activate transcription factors, which, in turn, promote the expression of genes encoding for proteins, that play a crucial role in restoring of neuronal functions involved in mood regulation.

Keywords: Antidepressant; Mechanism of action; Monoamine; Neuropeptide; Intracellular signaling; Transcription factor

1. Introduction

The first effective antidepressant drugs: a monoamine oxidase-inhibitor, iproniazid, and a tricyclic inhibitor of noradrenaline and serotonin uptake, imipramine, were discovered serendipitously, but once their clinical effectiveness had been established the new compounds of a similar mechanism of action were synthesized and introduced into clinic. Together with electroconvulsive treatment, which was introduced in the 1930's, these compounds brought a therapeutic progress and largely contributed to the decline in number of patients kept in psychiatric hospitals and institutions.

The progress in the field of drug treatment and seismotherapy was considerable. Electroconvulsive treatment is now administered under anesthesia and muscle relaxation, and is applied unilaterally, with no loss of efficacy. The new perspectives for physical therapy of depression were opened by rapid transcranial magnetic stimulation — a procedure much more satisfactory for the patient and acceptable for public opinion (Zyss, 1994). The treatment produces neurochemical effects similar to those induced by electroconvulsive treatment (Fleischman et al., 1995; Zyss et al., 1997) and the clinical results were favorable (George et al., 1995, 1997; Pascual-Leone et al., 1996).

The progress is visible also with antidepressant drug treatments. The initial irreversible monoamine oxidase inhibitors that blocked the activity of both monoamine oxidase-A and monoamine oxidase-B isoforms were replaced initially by still irreversible, but selective drugs, such as clorgyline, a monoamine oxidase-A inhibitor, or selegiline (a monoamine oxidase-B inhibitor that was found useful in Parkinson's disease rather than in depression), and then by reversible, monoamine oxidase-A-specific inhibitors, such as moclobemide.

A progress was also achieved within monoamine uptake inhibitors. The early compounds, such as imipramine, desipramine or amitriptyline, which inhibited both, although to different extent, the uptake of noradrenaline and serotonin, and, in addition, antagonized several neurotransmitter receptors, were to some degree replaced by drugs that either inhibited selectively serotonin uptake (SSRI) but still interacted with several receptors (e.g., fluoxetine, paroxetine, citalopram), or inhibited both noradrenaline and serotonin uptake, but possessed no receptor activity (e.g., venlafaxine). In addition, several atypical antidepressants, such as, e.g., mianserin, were introduced and still

* Corresponding author. Tel: +48-2-6360985; fax: +48-12-6374500.
E-mail address: nfvetula@cyf-kr.edu.pl (J. Vetulani).

0014-2999/00/$ - see front matter
PII: S0014-2999(00)00565-3

have their clinical position (see: Vetulani, 1997). It should be also noted that the old tricyclic antidepressants, such as amitriptyline, are still widely used. The important point, both from the theoretical and practical point of view, is that the effectiveness of the available treatments is still relatively low. Moreover, all known treatments alleviate the symptoms of depression only after a considerable delay period.

While the results of the search for an effective and rapid antidepressant therapy are still not fully satisfactory, the research in this field contributed immensely to the development of neuroscience, because of attempts to formulate several theories of antidepressant drug action.

2. Early hypotheses on action of antidepressants

The discovery that iproniazid and other hydrazine derivatives were monoamine oxidase inhibitors that effectively elevated the cerebral levels of noradrenaline and serotonin, immediately implicated those amines in etiology of depression. The finding that effective tricyclic antidepressants do not elevate the cerebral levels of biogenic amines posed initially some difficulties, till Sulser and Dingell (1968) proved that the drugs inhibit the reuptake of monoamines, and in this manner increase their availability at the receptor site. Thus, the common denominator of the action of both monoamine oxidase inhibitors and tricyclic drugs was the elevation of concentration of biogenic amines in the synaptic cleft. This was regarded as essential for their clinical activity. The findings that reduction of the brain content of biogenic amines, e.g., with reserpine, brought about depression, strengthened the hypotheses about the importance of monoamines in mood disorders and their participation in the mechanism of action of antidepressant drugs. The first hypotheses assumed that the neurotransmitter of crucial importance is either noradrenaline (Bunney and Davis, 1965; Schildkraut, 1965) or serotonin (Coppen, 1969).

The obstacle to assume a simple relationship between the monoamine concentration at the receptor site and the level of mood was the fact that antidepressant drugs do not elevate mood in normal, healthy subjects, and that in depressed patients they did not alleviate depression immediately, but a treatment lasting for at least two weeks is necessary (Oswald et al., 1973). This prompted us to carry out animal experiments with chronic administration of antidepressants, looking for the effects that appear only after a few weeks' treatment (Vetulani and Sulser, 1975)

3. The rise of the β-adrenoceptor downregulation hypothesis

Our experiments in which rats were injected with antidepressant compounds daily for periods ranging between 1 and 8 weeks demonstrated that all tested antidepressants (desipramine, iprindole, monoamine oxidase inhibitors) and electroconvulsive shock (ECS) downregulated the response of cyclic AMP generating system in cerebral slices to adrenergic stimulation, but only after a treatment lasting for four weeks and more. The initial assays were carried out on the slices from the "limbic forebrain" and the effect was relatively small, but now we know that our choice of the structure to investigate was not optimal. Further studies, carried out on cortical slices, confirmed our data concerning cyclic AMP response, and it was later found that the density of cortical β-adrenoceptors after chronic antidepressant treatment also declines (Banarjee et al., 1977). These findings were the basis of the so-called β-adrenoceptor downregulation hypothesis, which assumed that the suppression of signaling through β-adrenoceptors is indispensable for clinical antidepressant effects (Sulser et al., 1978). The hypothesis was generally accepted as several other antidepressant treatments, including an atypical antidepressant iprindole, were found to reduce the cyclic AMP response or the density of β-adrenoceptors in the cerebral cortex or its particular areas. The point was strengthened by the fact that depressogenic treatments, such as administration of reserpine and central chemosympathectomy, produced opposite changes that were reversible by electroconvulsive treatment (Vetulani et al., 1976).

4. The decline of β-adrenoceptor downregulation hypothesis and rise of alternative receptor theories

The original β-adrenoceptor downregulation hypothesis was soon challenged since several newly introduced antidepressants, particularly selective serotonin uptake inhibitors, did not produce β-adrenoceptor downregulation, and some of them, such as citalopram, may even produce an opposite effect (Nalepa and Vetulani, 1993a). Moreover, several antidepressants induced many neurochemical changes, and some of them were also observed only after a prolonged treatment, fitting the paradigm that only slowly developing changes may be related to the mechanism of therapeutic action of antidepressants.

Recent in vivo studies have established that, notwithstanding β-adrenoceptor downregulation, long-term antidepressant treatments lead to sustained activation of the cyclic AMP system in specific brain regions that leads to activation of cyclic AMP response element-binding protein (CREB) (Duman et al., 1997a,b).

Owing to that, there appeared several alternative hypotheses on the mechanism of action of antidepressants. Initially, we elaborated further the original β-adrenoceptor downregulation hypothesis by assuming the additional involvement of either α_2-adrenoceptor downregulation (Pilc and Vetulani, 1982) or α_1-adrenoceptor upregulation (Vetulani et al., 1984). Meanwhile the groups of Sulser

and Costa demonstrated that serotonergic system plays a permissive role for β-adrenoceptor downregulation development (Brunello et al., 1982; Janowsky et al., 1982).

5. The serotonin hypothesis

The real boost for serotonin hypothesis was the discovery of high clinical efficacy of antidepressants that selectively block the serotonin reuptake, with negligible effect on noradrenergic system. The interest in selective serotonin reuptake inhibitors was aroused in mid 1970's. The first compounds of this group were fluoxetine (Fuller et al., 1974), trazodone (Lehmann et al., 1975; Mann et al., 1980) and zimelidine (Ross et al., 1976; Benkert et al., 1977; Ogren et al., 1981), which were used as antidepressant agents by 1980 (Shopsin, 1980). At the same time , citalopram was discovered as a serotonin reuptake inhibitor with antidepressant potential (Christensen et al., 1977; Hyttel, 1977), but for a long time, it remained only an investigational drug before its recent successful introduction to clinic. By 1990, the research was carried out on further selective serotonin reuptake inhibitors, such as sertraline (Koe et al., 1983) and paroxetine (Danish University Antidepressant Group, 1990).

Although there exists a debate whether selective serotonin reuptake inhibitors are as potent as classical antidepressants (most psychiatrists today agree, however, that they should be used as the drugs of first choice), the selective serotonin reuptake inhibitors are attractive because they produce much fewer unwanted side-effects than classical tricyclics. Moreover, it was reported that using selective serotonin reuptake inhibitors together with 5-HT_{1A} receptor antagonists the course of remission may be shortened. Administration of pindolol, a 5-HT_{1A} and β-adrenoceptor antagonist, accelerated the action of selective serotonin reuptake inhibitors (Artigas et al., 1994). This acceleration was attributed to the blockade of 5-HT_{1A} receptors on serotonin neurons in the raphe nuclei, which inhibit serotonin release from the nerve ending (Romero et al., 1997). The question whether β-adrenoceptor blocking properties contribute to the effect of pindolol was answered (negatively) by the study of Zanardi et al. (1997). In connection with serotonin hypothesis, also the α_2-adrenoceptor downregulation hypothesis has been revitalized by the group of De Montigny, who postulated that downregulation of α_2-heteroceptors controlling serotonin release may be an important factor of antidepressant action (Mongeau et al., 1994)

6. Dopaminergic hypothesis

Playing a central role in the reward system (Koob, 1996), dopamine was a natural candidate for a neurotransmitter involved in the etiology of depression and mechanism of the action of antidepressant drugs. The first hypothesis implicating dopamine in depression and mania was proposed over 25 years ago (Randrup et al., 1975). Although it became disregarded soon, particularly because amphetamine was not found to be a suitable antidepressant, the next two decades brought some evidence that dopamine may be involved in depression. In a series of studies that began in early 1980's, Maj et al. demonstrated that almost all chronic antidepressant treatments increase the responses to dopaminergic simulation (e.g., Maj, 1984; Maj et al., 1984, 1987, 1989a). The evidence for dopamine involvement in the mechanism of action of antidepressants available a decade ago was presented by Kapur and Mann (1992), and more recently by Willner (1997). Although several studies indicated that behavioral responses to dopaminergic stimulation are increased by antidepressant treatments (e.g., Maj et al., 1989b), and, in particular, by electroconvulsive treatment (Wielosz, 1981; Antkiewicz-Michaluk et al., 1994), no correlation of this effect with changes in dopamine receptor binding could be found in earlier investigations. However, the recent studies of Maj et al., (1996, 1998), employing agonist rather than antagonist ligands, suggest that antidepressant treatments may increase the density of dopamine D_2 and dopamine D_3 receptors present in active conformation. Several (but not all) antidepressants were then reported to increase the expression on mRNA coding for dopamine D_2 dopamine receptors in limbic structures of rat brain (Dziedzicka-Wasylewska et al., 1997; Ainsworth et al., 1998). The relationship between the increased agonistic binding to dopamine receptors and clinical antidepressant action is, however, uncertain, as the increases in binding of dopamine dopamine D_2 and dopamine D_3 receptor agonists takes place rapidly and, in some cases, the increase is more prominent 2 h after a single dose than after repeated treatment (Rogoz and Dziedzicka-Wasylewska, 1999). In contrast to adrenoceptors, whose specific involvement in depression has not been defined, the dopaminergic system may be involved in the functioning of reward system, which most probably is compromised in depression.

7. Glutamatergic system and the NMDA receptor

An important discovery of the group of Skolnick was the finding that NMDA receptor changes may be involved in the action of antidepressant drugs. Since early 1990's evidence accumulated that functional NMDA receptor antagonists act as antidepressants. This was demonstrated both in the chronic mild stress model of depression (Papp and Moryl, 1994) and in forced swim test (Trullas and Skolnick, 1990; Maj et al., 1992) (see also Skolnick, 1999). Further studies demonstrated also that antidepressant treatments inhibit some functions of the NMDA receptor, e.g., NMDA-evoked acetylcholine release (Kiefer et al., 1999). The most convincing evidence for importance

of interaction of antidepressants with NMDA receptor was the demonstration in Skolnick's laboratory that clinically active antidepressants almost invariably downregulate the strychnine-insensitive glycine receptors in neocortical membranes, as demonstrated by reduction of the potency of glycine to inhibit [^{3}H]-5,7-dichlorkynurenic acid binding (Paul et al., 1994). The depression of glutamatergic transmission by chronic antidepressants is the result of reduction of the proportion of high activity glycine sites on NMDA receptor (Skolnick et al., 1996).

The NMDA receptor antagonists were similar to classical antidepressants in respect of induction of β-adrenoceptor downregulation (Paul et al., 1992; Layer et al., 1995, see also Skolnick et al., 1996). Conversely, functional noradrenergic system is necessary for the reduction by antidepressants of the activity of glycine site on NMDA receptor (Harkin et al., 2000). An interesting finding of Wedzony et al. (1995) was the demonstration that the development of β-adrenoceptor downregulation by an NMDA receptor antagonist CGP may be facilitated by stress of the forced swimming. This suggests that antidepressant effects may be influenced by environmental conditions. The observation that forced swim test increased the potency of glycine at the NMDA receptor complex glycine site (Nowak et al., 1995) confirmed the importance of stress on the development of antidepressant activity of drug treatment.

The adaptive changes of NMDA receptor induced by chronic antidepressant administration are reflected at the level of gene expression. ECS increases the mRNA coding for some NMDA receptor subunits (NR2A in many regions) but decreased that for mGluR5b (Watkins et al., 1998). Generally, long-term antidepressant treatment produces region-specific changes in expression of transcripts for NMDA receptor subunits, presumably altering NMDA receptor composition. Various antidepressants differ in their action in this respect (Boyer et al., 1998). A discussion of the role of NMDA receptor adaptation for antidepressant action was presented by Huang et al. (1997).

The NMDA receptor is a ligand-dependent Ca^{2+} channel, and therefore regulates Ca^{2+} influx and, consequently, nitric oxide (NO) synthesis. Thus, some effects mediated by NMDA receptor complex may, in fact, result from changes in intracellular Ca^{2+} and NO concentration. In fact Ca^{2+} antagonists were found to produce an effect similar to antidepressants on NMDA receptor complex glycine site (Nowak et al., 1993). It has also been found that NO synthase (NOS) inhibitors, similarly to NMDA receptor antagonists, produce antidepressant-like effect in the forced swimming test in mice and may have a potential of antidepressant agents (Harkin et al., 1999). On the other hand, chronic ECS increases the NOS activity in the cerebral cortex, cerebellum and hippocampus, and this effect may be regarded as a compensatory mechanism to counteract the reduced NMDA receptor complex reactivity (Nowak et al., 1997).

8. Neuropeptides

Although for the last four decades the action of antidepressants was regarded as closely associated with monoamine transmission systems, and in the last decade the role for excitatory amino acids was pointed out, the possible involvement of neuropeptides has not been taken into account, in spite of the fact that the seminal works of de Wied brought attention to the biological role of this class of neuromodulators that are now implicated in almost every function of the central nervous system. While their roles in memory and social interactions were particularly studied, the participation of neuropeptides in regulation of mood and etiology of depression should not be overlooked. Recently, it has been discovered that drugs acting on some peptidergic systems have a considerable potential as antidepressants.

The role for neuropeptides in regulation of mood and memory is twofold. It might result from the modulation of the action on monoamine transmitters with which they coexist in a neuron (e.g., substance P and thyrotropin-releasing hormone (TRH) in the serotonergic raphe neurons). As a single neuron may secrete both a neurotransmitter and one or more neuropeptides, thus corelease combined with multiple receptors provides the means for greatly amplifying the complexity of actions and the levels of control at a single synapse. The second important route of action of peptides on mood may be related to their role played in regulation of hormonal systems.

8.1. Individual peptides

8.1.1. Substance P

Substance P a long time after its discovery as the first peptide having neurotransmitter functions, aroused recently a considerable interest because of antidepressant properties of antagonists of its preferred binding site, the tachykinin NK_1 receptor receptor. In the human brain substance P coexists with serotonin in raphe neurons (Baker et al., 1991), and tachykinin NK_1 receptor receptor is the predominant tachykinin receptor (Dietl and Palacios, 1991). Unfortunately, the substance P distribution, coexistence with serotonin, and distribution of tachykinin receptors in the primate brain is different from those in mice and rats. Owing to that the studies on the possible antidepressant properties of tachykinin NK_1 receptor receptor antagonists are difficult, because the role of substance P in the control of mood of humans may be different to that in rodents.. Although gerbils and guinea pigs have the characteristics of the substance P system similar to that of primates, those species are much less used in psychopharmacology. tachykinin NK_1 receptor receptor antagonists, such as compound L-733 060, now are studied clinically as potential antidepressants (Kramer et al., 1998). Clinical studies

of an substance P receptor antagonist MK-869 and related compounds are also promising (Baby et al., 1999). The target of possible antidepressant action of substance P receptor antagonists seem to be amygdala (Smith et al., 1999).

The role of substance P as a depressogenic agent is also suggested by the fact that several antidepressants given chronically reduce the substance P content in the striatum, substantia nigra and amygdala (Shirayama et al., 1996). This raises the possibility that such a decrease may contribute to the therapeutic action of antidepressants in affective disorders. If one would like to use some poetry, he might say that substance P is the mediator of not only physical, but also of the mental pain.

8.1.2. TRH

Since the 70's, TRH was suspected to possess antidepressant properties. We were investigating it briefly for the ability to produce β-adrenoceptor downregulation, but as its effect, unlikely that of other antidepressant treatments, appeared rapidly but disappeared during more prolonged TRH administration (Vetulani et al., 1975), this line of research, unfortunately, was abandoned. Only after more than 20 years, it was demonstrated that TRH and its analogue, pGlu–Glu–Pro–NH_2, decrease the floating time in the Porsolt's test, and that synthesis of both peptides in limbic regions is induced by ECS (Pekary et al., 1999; Sattin, 1999). The reduction of floating time was described also for prepro-TRH 178-199 (Redei et al., 1999). Following controlled clinical studies have revealed that TRH when injected intrathecally may rapidly, though transiently (for 2–3 days), induce remissions of major depression. This is of particular interest in the light of well-known phenomenon of delayed response to antidepressant treatments (Sattin, 1999). Sattin suggests that TRH and related peptides are likely to play a significant role in the inhibition of glutamatergic subcortical limbic neurons, which may be hyperactive in depression. One of the mechanisms of action of electroconvulsive treatment may consist of augmenting this inhibition because of induction of synthesis of TRH in specific limbic and frontal cortical regions. The antidepressant action of tricyclics and atypical antidepressant may be due, according to him, to activation of a subset of γ-amino bytyric acid (GABA)-ergic interneurons, which then inhibit the pathologically hyperactive glutamatergic limbic neurons.

8.1.3. Neuropeptide Y

Neuropeptide Y is widely distributed in central and peripheral neurons. In sympathetic postganglionic neurons, Neuropeptide Y coexists with noradrenaline. The peptide, acting prejunctionally, suppresses the release of noradrenaline from sympathetic nerve terminals (Wahlestedt and Hakanson, 1986). The action of neuropeptide Y in the hypothalamic control of the pituitary–adrenocortical axis, suggested by earlier immunocytochemical studies was confirmed by Wahlestedt et al. (1987). who found that injections of neuropeptide Y into the area of the periventricular nucleus of the hypothalamus of freely moving rats elevated the levels of adrenocorticotrophic hormone (ACTH) and corticosterone and caused activation of pituitary–adrenocortical axis.

Studies on humans have suggested that neuropeptide Y is involved in major depression and anxiety. The reduced cerebrospinal fluid concentrations of neuropeptide Y found in patients with major depression may reflect disturbed synthesis, turnover or degradation of neuropeptide Y in this illness (Widerlov et al., 1988).

The hypothesis that neuropeptide Y might be involved in the pathophysiology of depressive illness was also supported by finding that treatment with ECS increases the neocortical and hippocampal neuropeptide Y-like immunoreactivity (Wahlestedt et al., 1990), while imipramine elevates the immunoreactivity in the frontal cortex and hypothalamus (Heilig et al., 1988). Recently, the antidepressant-like effect of neuropeptide Y has been demonstrated in the forced swim test in rats (Stogner and Holmes, 2000).

8.1.4. Vasopressin and oxytocin

The psychotropic effects of vasopressin and oxytocin are well known thanks to classical works of de Wied (cf. de Wied and van Ree, 1989). Recently, the role of vasopressin in depression is discussed in view on its effect on the hypothalamic–pituitary axis and role in the stress that may be an important factor in etiology of depression (Scott and Dinan, 1998). Both vasopressin and oxytocin acted similarly to antidepressants in behavioral and biochemical animal tests (Arletti and Bertolini, 1987; Nalepa and Vetulani, 1990; Popik and Vetulani, 1993; Arletti et al., 1995). It has been postulated that an important component of the action of atypical antidepressants is the release of oxytocin (Uvnas-Moberg et al., 1999).

8.2. Endocrine systems and antidepressants

A relationship between endocrine illnesses and depression has been noted since years and many data indicate functional disturbances of endocrine systems in depression. Particularly affected are: hypothalamic–pituitary–adrenal axis, hypothalamic–pituitary–thyroid axis, neuropituitary axis and somatotropic axis (for review, see Holsboer et al., 1992, Ansseau, 1997).

The hypothalamic–pituitary–adrenal axis comprises corticotropin-releasing hormone (CRH), released from nerve terminals in the median eminence of the hypothalamus and transported in the hypothalamo–hypophyseal portal system to the corticotrophs, where it increases the release of ACTH and other proopiomelanocortin-derived compounds. In addition, the secretion of ACTH is positively modulated by arginine vasopressin. ACTH runs to

the adrenal cortex, where it stimulates the synthesis and secretion of glucocorticoids. Among adrenal steroids, corticosterone is the major negative feedback signal in the regulation of ACTH, affecting hippocampus, hypothalamus, pituitary at the genomic and nongenomic level. Corticosterone binds to two types of receptors: with high affinity to the mineralocorticosteroid receptor (MR) that are located predominantly in the hippocampus, and with affinity sixfold to tenfold lower to the glucocorticoid receptor (GR) that are distributed throughout the brain. Occupation of hippocampal MRs maintains excitability and limbic inhibitory control over the hypothalamic–pituitary–adrenal system. GR activation induced by higher level of corticosterone counteracts the action of MR. Thus, the degree of hippocampal inhibition of the hypothalamic–pituitary–adrenal axis depends on the level of circulating corticosterone. Noradrenaline, serotonin and acetylcholine enhance the secretory activity of the hypothalamic–pituitary–adrenal system, whereas GABA inhibits it.

Depression is often associated with the hyperactivity of hypothalamic–pituitary–adrenal axis. This hyperactivity normalizes in the course of successful antidepressant treatment (Pepin et al., 1992b; Barden et al., 1995). The failure to normalize the activity of hypothalamic–pituitary–adrenal axis by antidepressant treatment indicates a poor prognosis and this observation demonstrates a link between actions of antidepressants on neuroendocrine systems and their therapeutic effects (cf. Holsboer et al., 1992).

The antidepressant administration influences the expression of genes encoding for hypothalamic–pituitary–adrenal axis constituents. Thus, chronic treatment with some tricyclic antidepressants downregulates the CRH mRNA in the paraventricular nucleus (Brady et al., 1991) and upregulates the hippocampal MR (Brady et al., 1991) and the GR mRNA (Peiffer et al., 1991; Rossby et al., 1995). However, the latter effect is not a common mechanism of antidepressants, as the most widely used selective serotonin reuptake inhibitor, fluoxetine does not cause such an effect (Rossby et al., 1995).

Elevated baseline cortisol, dexamethasone nonsuppression and blunted CRH/ACTH release in depression have been well documented. The finding of elevated levels of vasopressin in postmortem studies of depressives and the lowering of cerebrospinal fluid vasopressin levels by antidepressants raises the question of the precise role of vasopressin in the overactivity of the hypothalamic–pituitary–adrenal axisin depression (Scott and Dinan, 1998). Stress-induced regulation of locus coeruleus sensitivity to CRH may underlie behavioral aspects of stress-related psychiatric disorders. Recent data originated from animal models suggest that swim stress (and perhaps other stressors) functionally alters CRH receptors that have an impact on locus coeruleus activity (Curtis et al., 1999). Results obtained by Mansbach et al. (1997) suggest the potential efficacy of CRF receptor antagonists in the treatment of affective disorders.

9. Biochemical hypotheses of affective disorders and intracellular effects of antidepressant treatments

In the last few years, an explanation of the etiology of depression has been sought on the level of the interdependence between systems of second messengers, G proteins and protein kinases. Thus, Wachtel (1989) suggested that affective disorders occur as the result of imbalance of the two major intraneuronal messenger systems, the adenylyl cyclase and phospholipase C, with depression resulting from hypofunction of cyclic AMP pathway associated with a relative predominance of inositol trisphosphate (IP_3)-diacylglicerol (DG) system, while mania results from the converse.

Important results were obtained in studies on nonneuronal tissue, namely on leukocytes of patients with depression by Avissar and Schreiber, who assumed that the processes in leukocytes resemble those taking place in cerebral neurons. Avissar and Schreiber (1992) reviewed the role G proteins in the etiology of affective disorders and antidepressants action. They found a significant elevations in of $G_{\alpha s}$ and $G_{\alpha i}$, levels in mononuclear leukocytes of manic patients, and reduction in $G_{\alpha s}$ and $G_{\alpha i}$ in patients with bipolar depression (Avissar et al., 1997). Moreover, the low levels of G protein function and immunoreactivity were normalized by electroconvulsive treatment (Avissar et al., 1998), and light therapy (Avissar et al., 1999). These results are consistent with blunting of β-adrenoceptor mediated protein kinase A response in fibroblasts from patients with major depression (Manier et al., 1996; Shelton et al., 1996, 1999) and reduction of adenylyl cyclase immunolabeling and activity in postmortem temporal cortex of depressed suicide victims (Reiach et al., 1999). Lesch and Manji (1992) demonstrated that chronic antidepressants modify differently mRNA of various subtypes of Galpha protein in rat brains, thus modifying the balance between various signal pathways.

10. The interference of antidepressant treatment with dialogue between systems of protein kinases

Receptors of neurotransmitters that initiate signaling cascades associated with protein kinase A and protein kinase C may mutually control themselves. This phenomenon is known as receptor systems' crosstalk or dialogue.

Basing on our findings, we have proposed that the protein kinase C-related processes, including a dialogue between α_1 and β-adrenoceptors, are among the targets for antidepressant drug action (Nalepa, 1994). The possibility of cooperation of α- and β-adrenoceptors was firstly suggested by the observation of Blumberg et al. (1976), who noticed that isoproterenol, a selective β-adrenoceptor agonist, stimulated generation of cyclic AMP less than did noradrenaline, which activates all types of adrenoceptors.

Daly et al. (1980, 1981) described the potentiation of the β-adrenoceptor response by α-adrenoceptors in the cerebral cortex. Further research revealed a relation between the metabolism of inositol phospholipids and neurotransmitter-stimulated generation of cyclic AMP (Karbon et al., 1986; Duman and Enna, 1987; Enna and Karbon, 1987). Although the mechanism of this potentiation was not definitively explained, the authors agreed that one of the most serious candidates for the role of amplifier of cyclic AMP response after β-adrenoceptor stimulation was the phosphorylating activity of protein kinase C (Houslay, 1991; Tanaka and Saito, 1992). Some authors suggest that protein kinase C phosphorylates the G_i protein (coupled to the α_2-adrenoceptor) counteracting the inhibition of cyclic AMP generation (Katada et al., 1985; Jakobs et al., 1986), while others assume that protein kinase C acts on G_s protein of the β-adrenoceptor, potentiating the cyclic AMP response (Sugden and Klein, 1988). Regardless the real targets of protein kinase C action, the final effect would be the enhancement of the cyclic AMP response.

Protein kinase C activation occurs after stimulation of receptors that operate through phosphatidylinositols cascade, e.g., α_1-adrenergic and 5-HT_2 receptor families. In addition to G proteins, the proteins of adrenoceptors are among intracellular substrates of protein kinase C. For example, protein kinase C phosphorylates the protein of the α_1-adrenoceptor (Leeb-Lundberg et al., 1985) decreasing its sensitivity and reducing generation of inositol phosphates (Nalepa and Vetulani, 1991a).

Chronic treatment with ECS and imipramine has been reported to increase the density of α_1-adrenoceptors (Vetulani et al., 1983, 1984). Subsequently, the shift of the balance between α_1- and β-adrenoceptors towards α_1-adrenoceptors was postulated to be a characteristic effect of chronic antidepressant treatments (Vetulani, 1984) and it has been suggested that protein kinase C-related processes play the main role in this phenomenon (Nalepa, 1994). Nevertheless, the increased density of α_1-adrenoceptors that occurred after ECS and imipramine was not accompanied by the increase in inositol phosphate response to noradrenaline (Nalepa and Vetulani, 1993a). Moreover, we found that chronic mianserin and citalopram enhanced the responsiveness of α_1-adrenoceptors without changes in the receptor density (Nalepa and Vetulani, 1993b, 1994). Our results show that protein kinase C is responsible for the dialogue between α_1- and β-adrenoceptors and indicate that both processes, the protein kinase C-α_1-adrenoceptor negative feedback and the protein kinase C-induced potentiation of β-adrenoceptor response, are among the targets for antidepressant drugs (Nalepa and Vetulani, 1991a,b, 1994, 1996; Nalepa et al., 1993) but not of antipsychotics (Nalepa, 1993). Thus, we proposed that a counter-regulation of the physiological negative feedback between protein kinase C and α_1-adrenoceptor may occur as result of chronic treatment with antidepressants, and this effect may lead to the prolonged activation of this receptor (Nalepa and Vetulani, 1991a; Nalepa et al., 1993, 1996). The latter process may counteract the β-adrenoceptor down regulation of cyclic AMP response to agonists (Nalepa and Vetulani, 1991b). In fact, a counter-regulation between protein kinase C and protein kinase A on agonist-induced desensitization of β-adrenoceptor system has been demonstrated in various cell lines (Shih and Malbon, 1994). Thus, Nalepa (1994) postulated that taking into consideration the role of protein kinase C in the crosstalk of phospholipase C and adenylyl cyclase-related systems explains why, despite the antagonization of α_1-adrenoceptor and β-adrenoceptor down regulation by some antidepressants, an enhancement of the process of noradrenergic transmission may take place as a final effect of these drugs. The interaction occurring at the level of second messenger systems may determine both the ultimate effectiveness of drug and the emergence of depression (Nalepa, 1994). As the activation of protein kinase C and protein kinase A can be induced by both noradrenaline and serotonin signaling pathways, cooperation of these two systems may occur at the intracellular level.

Recent studies on an serotonin and noradrenaline reuptake inhibitors venlafaxine provide evidence for a crosstalk between noradrenergic and serotonergic receptor cascades at the level of mechanisms involved in the desensitization of the β adrenoceptor-coupled adenylate cyclase system (Nalepa et al., 1998). These studies showed that repetitive treatment with venlafaxine failed to alter in normal animals either the density of β-adrenoceptors or the response of the β-adrenoceptor-coupled cyclic adenylate cyclase system to noradrenaline, but significantly decreased the cyclic AMP response to noradrenaline in the brain of rats with selective depletion of brain serotonin by *p*-chlorophenylalanine.

The receptor dialogue hypothesis explains two important points of the action of antidepressants: an increase in the intracellular cyclic AMP in vivo, observed by Duman's group (Nibuya et al., 1996), and discrepancies between the changes at the receptor, second messenger and behavioral level.

11. Antidepressant treatments and phosphorylation of intracellular proteins

Phosphorylation, effected by messenger-regulated protein kinases, is the main route of activation or deactivation of cellular proteins. Antidepressant treatments were found to interfere with intracellular phosphorylation processes and this action may contribute to explanation of the therapeutic effects (Popoli et al., 2000). First reports were published a decade ago, when Perez et al. (1991) reported the increased phosphorylation of the cyclic AMP binding protein associated with the crude microtubule fraction of rat cerebral cortex after prolonged treatment with different antidepressants, such as fluoxetine and (+)-oxaprotiline.

Also, chronically administered fluvoxamine enhanced the phosphorylation of a microtubule-associated protein 2 (Perez et al., 1995). The chronic treatment with a monoamine oxidase-A-inhibitor, moclobemide, increased significantly the binding of cyclic AMP to cyclic AMP-dependent protein kinase A in rat cerebral cortex (Mori et al., 1998). A long-term treatment with two selective serotonin reuptake inhibitor, paroxetine and fluvoxamine, and with an serotonin and noradrenaline reuptake inhibitors, venlafaxine, induced a large increase of Ca^{2+}/calmodulin-dependent protein kinase II autophosphorylation in synaptic vesicles and synaptic cytosol in the hippocampus, but not in synaptosomal membranes (Popoli et al., 1995). This suggested that only presynaptic kinase was affected by chronic antidepressants. These findings may be relevant for desensitization of presynaptic 5-HT autoreceptors and adaptive changes in the molecular machinery regulating transmitter release at serotonergic terminals. A classic tricyclic, imipramine, and ECS, in contrast to selective serotonin reuptake inhibitors and venlafaxine, induced a significant increase in the CaM-II activity in the particulate fraction from the hippocampus (Pilc et al., 1999).

The results showing the action of chronic antidepressant treatments on various kinases are of particular interest, as transcription factors are their important targets.

12. Genomic changes

The slowness in development and persistence of the clinical effect of antidepressants suggest that antidepressant treatments affect the gene transcription. Various antidepressants may influence different intracellular signal cascades and alter their interrelationships, e.g., at the level of protein kinases. However, from the biological point of view, only the end-result of an antidepressant treatment counts, and, in all cases, it may be identical because of convergence of the intracellular signals. This convergence occurs at the level of transcription factors, whose transcriptional activities are regulated by the convergent activities of various protein kinases including protein kinase A, protein kinase C, Ca^{2+}/calmodulin-dependent protein kinase II and others. Transcription factors recognize and bind to the specific sequences, DNA response elements, in the promotor regions of genes, in this way, changing the rate of expression of target genes.

Various classes of antidepressants increase the expression of CREB (Nibuya et al., 1996). Among the multiple target genes that could be regulated by CREB is brain-derived neurotrophic factor (BDNF) (Duman, 1998). Chronic administration of several types of antidepressant drugs increases expression of BDNF and its receptor TrkB (Nibuya et al., 1995). BDNF is a neurotrophin and plays an important role in survival and function of neurons (Lindsay et al., 1994). Many data suggest that neurotrophin function is altered in stress-related affective disorders, and that BDNF could be involved in the etiology and treatment of these illnesses (Duman, 1998). Although the hypothesis that antidepressant treatments lead to an increase in neurotrophin levels because of activation of CREB (Duman et al., 1997b) is attractive, there emerge some data not consistent with it. Thus chronic treatment with venlafaxine did not elevate the mean steady-state level of CREB mRNA and significantly reduced the amount of phosphorylated CREB in nuclear lysates of the rat cortex (Rossby et al., 1999).

The "serotonin/noradrenaline/glucocorticoid link" hypothesis of affective disorders and the action of antidepressants, postulated by Pryor and Sulser (1991), has integrated glucocorticoid receptor system into amine hypothesis of affective disorders. Functional link between aminergic and endocrine signaling (glucocorticoids) beyond the receptors has been demonstrated in C6 glioma cells at the level of preproenkephalin gene expression (Yoshikawa and Sabol, 1986; Eiring et al., 1992). In vivo, the regulation of preproenkephalin gene expression depends on serotonin, as chronic fluoxetine enhanced the expression of preproenkephalin mRNA in the rat amygdala, and this effect disappeared in rats with depleted level of brain serotonin (Rossby et al., 1996).

Some antidepressants, e.g., desipramine, induce also increases in glucocorticoid receptor gene promoter activity and glucocorticoid receptor mRNA levels (Pepin et al., 1992a; Rossby et al., 1995), and in the receptors density (Przegalinski and Budziszewska, 1993). However, other antidepressants, such as oxaprotiline, citalopram and mianserin did not affect the receptor density (Budziszewska et al., 1994).

Soluble cytoplasmic glucocorticoid receptors are known to act as transcription factors. Frechilla et al., (1998) demonstrated a differential and region-specific effect of chronic antidepressant treatments on the DNA-binding activities. The chronic treatments with two antidepressants, fluoxetine and desipramine, differently affecting monoamine reuptake, produced a similar effect on DNA response elements in the frontal cortex, causing an increase the binding activity of nuclear proteins to cyclic AMP response element (CRE) and decreasing substance P1 consensus binding. On the other hand, in the hippocampus only fluoxetine treatment caused changes in CRE and SP1 consensus binding, while desipramine treatment did not affect it. In contrast, glucocorticoid response element (GRE) binding activity was enhanced in the hippocampus by desipramine but not fluoxetine. The authors concluded that the lack of action of desipramine treatment on hippocampal CRE and SP1 consensus binding was caused by the ability of desipramine to increase GRE binding activity. These results may exemplify the protein–protein interactions among various transcription factors and the effect of chronic antidepressant treatments on these interactions. Antidepressant drugs can also inhibit the CRE-directed

gene transcription that was stimulated by membrane depolarization (Schwaninger et al., 1995).

Lithium is a mood stabilizer, which is used in treatment of bipolar depression. Studies on the effects of chronic treatment with lithium clearly show that its most important action takes place downstream of receptors. Moreover, they indicate that action of lithium may involve different signaling cascades. Thus, similarly as neurotransmitters triggering intracellular signaling cascade, lithium may amplify and integrate signals in the central nervous system. Results obtained in human neuroblastoma cells demonstrate that lithium can influence the CREB functioning even if the expression of CREB remained unchanged (Wang et al., 1999). Same authors reported that chronic treatment with lithium inhibited phosphorylation of CREB and DNA binding induced by the adenylyl cyclase activator forskolin, but had no effect on constitutive expression of CREB protein. Accumulated evidence has identified the family of protein kinase C isozymes as targets for the long-term action of lithium. Chronic lithium administration reduces the expression of protein kinase C α and ε, as well as a major protein kinase C substrate, MARCKS, which has been implicated in long-term neuroplastic events in the developing and adult brain (Manji and Lenox, 1999). Subsequently, it was reported that lithium modulates AP-1 DNA binding activity and the expression of genes regulated by AP-1 and the lithium-induced increases in AP-1 DNA binding activity were accompanied by increases in *p*-c-Jun and c-Jun levels in SH-SY5Y cells (Yuan et al., 1999). The same paper indicated that chronic in vivo lithium administration increased AP-1 DNA binding activity in frontal cortex and hippocampus and also increased the levels of the phosphorylated, active forms of c-Jun NH2-terminal kinases (JNKs) in both brain regions.

13. Concluding remarks

Depression may be regarded as a chronic condition, caused by unfavorable genomic changes that may arise from various causes, including heredity, environmental stress or neurotoxicity, and lead to loss of plasticity of nervous mechanisms (Rossby and Sulser, 1997). Because of historical reasons we believe that most of those changes are related to monoamines, particularly to disturbances in noradrenergic and serotonergic transmission. The stress-related damage of hippocampal serotonin neurons, overexpression of β-adrenoceptor, and several other receptor changes were proposed to play a role in etiology of depression, although some of them may be in reality only epiphenomena. The antidepressant therapies cannot repair the genomic changes and return plasticity, but those that are effective may lead to changes that compensate for the loss (Rossby and Sulser, 1997).

The primary targets for antidepressant actions seem to be membrane receptors, but this is only the beginning: the prolonged action of receptors leads to changes in internal signaling cascades that converge at the level of nucleus and lead to genomic changes. Because of that convergence the drugs affecting different signaling pathways may eventually produce the same final effect, e.g., activation of CREB and resulting increase in neurotrophin synthesis (Duman et al., 1997a,b). However, as mentioned above, Rossby et al. (1999) have shown that at least one effective antidepressant does not conform to this pattern. As in the whole history of studies of antidepressants, a new attractive hypothesis is in a short time challenged by new findings, requiring a search for novel explanations.

The last development in the field of antidepressant is an increase interest in neuropeptides. Finally, this important group on neuromodulators, for the first time brought to our attention by David de Wied, entered the depression scene. The neglected for long time TRH may present a novel mechanism of antidepressant action, characterized by rapid onset. The antagonists on tachykinin NK_1 receptor receptor may also bring a considerable therapeutic progress.

The history of studies on antidepressants was a great challenge for neuroscientists and the research in this field brought a considerable progress in our understanding of the central nervous system mechanisms. The discovery of the involvement of peptides demonstrates that after more than forty years of research there is still a lot to be done.

References

Ainsworth, K., Smith, S.E., Zetterström, T.S., Pei, Q., Franklin, M., Sharp, T., 1998. Effect of antidepressant drugs on dopamine D_1 and D_2 receptor expression and dopamine release in the nucleus accumbens of the rat. Psychopharmacology (Berlin) 140, 470–477.

Ansseau, M., 1997. Hormonal disturbances in depression. In: Honig, A., van Praag, H.M. (Eds.), Depression: Neurobiological, Psychopathological and Therapeutic Advances. Wiley, Chichester, England, pp. 235–250.

Antkiewicz-Michaluk, L., Michaluk, J., Vetulani, J., 1994. Modification of effects of chronic electroconvulsive shock by voltage-dependent Ca^{2+} channel blockade with nifedipine. Eur. J. Pharmacol. 254, 9–16.

Arletti, R., Benelli, A., Poggioli, R., Luppi, P., Menozzi, B., Bertolini, A., 1995. Aged rats are still responsive to the antidepressant and memory-improving effects of oxytocin. Neuropeptides 29, 177–182.

Arletti, R., Bertolini, A., 1987. Oxytocin acts as an antidepressant in two animal models of depression. Life Sci. 41, 1725–1730.

Artigas, F., Perez, V., Alvarez, E., 1994. Pindolol induces a rapid improvement of depressed patients treated with serotonin reuptake inhibitors. Arch. Gen. Psychiatry 51, 248–251.

Avissar, S., Nechamkin, Y., Barki-Harrington, L., Roitman, G., Schreiber, G., 1997. Differential G protein measures in mononuclear leukocytes of patients with bipolar mood disorder are state dependent. J. Affective Disord. 43, 85–93.

Avissar, S., Nechamkin, Y., Roitman, G., Schreiber, G., 1998. Dynamics of ECT normalization of low G protein function and immunoreactivity in mononuclear leukocytes of patients with major depression. Am. J. Psychiatry 155, 666–671.

Avissar, S., Schreiber, G., 1992. The involvement of guanine nucleotide binding proteins in the pathogenesis and treatment of affective disorders. Biol. Psychiatry 31, 435–459.

Avissar, S., Schreiber, G., Nechamkin, Y., Neuhaus, I., Lam, G.K., Schwartz, P., Turner, E., Matthews, J., Naim, S., Rosenthal, N.E., 1999. The effects of seasons and light therapy on G protein levels in mononuclear leukocytes of patients with seasonal affective disorder. Arch. Gen. Psychiatry 56, 178–183.

Baby, S., Nguyen, M., Tran, D., Raffa, R.B., 1999. Substance P antagonists: the next breakthrough in treating depression? J. Clin. Pharm. Ther. 24, 461–469.

Baker, K.G., Halliday, G.M., Hornung, J.P., Geffen, L.B., Cotton, R.G., Tork, I., 1991. Distribution, morphology and number of monoamine-synthesizing and substance P-containing neurons in the human dorsal raphe nucleus. Neuroscience 42, 757–775.

Banarjee, S.P., Kung, L.S., Riggi, S.J., Chanda, S.K., 1977. Development of β adrenergic receptor subsensitivity by antidepressants. Nature 268, 455–456.

Barden, N., Reul, J.M., Holsboer, F., 1995. Do antidepressants stabilize mood through actions on the hypothalamic–pituitary–adrenocortical system? Trends Neurosci. 18, 6–11.

Benkert, O., Laakmann, G., Ott, L., Strauss, A., Zimmer, R., 1977. Effect of zimelidine (H 102/09) in depressive patients. Arzneimittelforschung 27, 2421–2423.

Blumberg, J.B., Vetulani, J., Stawarz, R.J., Sulser, F., 1976. The noradrenergic cyclic AMP generating system in the limbic forebrain: pharmacological characterization in vitro and possible role of limbic noradrenergic mechanisms in the mode of action of antipsychotics. Eur. J. Pharmacol. 37, 357–366.

Boyer, P.A., Skolnick, P., Fossom, L.H., 1998. Chronic administration of imipramine and citalopram alters the expression of NMDA receptor subunit mRNAs in mouse brain. A quantitative in situ hybridization study. J. Mol. Neurosci. 10, 219–233.

Brady, L.S., Whitfield, H.J. Jr., Fox, R.J., Gold, P.W., Herkenham, M., 1991. Long-term antidepressant administration alters corticotropin-releasing hormone, tyrosine hydroxylase, and mineralocorticoid receptor gene expression in rat brain. Therapeutic implications. J. Clin. Invest. 87, 831–837.

Brunello, N., Barbaccia, M.L., Costa, D.M., 1982. Down-regulation of beta adrenergic receptors following repeated injections of desmethylimipramine: permissive role of serotonergic axons. Neuropharmacology 21, 1145–1149.

Budziszewska, B., Siwanowicz, J., Przegalinski, E., 1994. The effect of chronic treatment with antidepressant drugs on the corticosteroid receptor levels in the rat hippocampus. Pol. J. Pharmacol. 46, 147–152.

Bunney, W.E., Davis, J.M., 1965. Norepinephrine in depressive reactions. Arch. Gen. Psychiatry 13, 483–494.

Christensen, A.V., Fjalland, B., Pedersen, V., Danneskiold-Samsoe, P., Svendsen, O., 1977. Pharmacology of a new phthalane (Lu 10-171), with specific 5-HT uptake inhibiting properties. Eur J Pharmacol. 41, 153–162.

Coppen, A.J., 1969. Biochemical aspects of depression. Int. Psychiatry Clin. 6, 53–81.

Curtis, A.L., Pavcovich, L.A., Valentino, R.J., 1999. Long-term regulation of locus ceruleus sensitivity to corticotropin-releasing factor by swim stress. J. Pharmacol. Exp. Ther. 289, 1211–1219.

Daly, J.W., Padgett, W., Creveling, C.R., Cantacuzene, D., Kirk, K.L., 1980. Fluoroepinephrines: specific agonists for the activation of alpha and beta adrenergic-sensitive cyclic AMP-generating system in rat slices. J. Pharmacol. Exp. Ther. 212, 382–389.

Daly, J.W., Padgett, W., Creveling, C.R., Cantacuzene, D., Kirk, K.L., 1981. Cyclic AMP-generating systems: regional differences in activation by adrenergic receptors in rat brain. J. Neurosci. 1, 45–59.

Danish University Antidepressant Group, 1990. Paroxetine: a selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study. J. Affect. Disord. 18, 289–299.

de Wied, D., van Ree, J.M., 1989. Neuropeptides: animal behaviour and human psychopathology. Eur. Arch. Psychiatry Neurol. Sci. 238, 323–331.

Dietl, M.M., Palacios, J.M., 1991. Phylogeny of tachykinin receptor localization in the vertebrate central nervous system: apparent absence of neurokinin-2 and neurokinin-3 binding sites in the human brain. Brain Res. 539, 211–222.

Duman, R.S., 1998. Novel therapeutic approaches beyond the serptonin receptor. Biol. Psychiatry 44, 324–335.

Duman, R.S., Enna, S.J., 1987. Modulation of receptor-mediated cyclic AMP production in brain. Neuropharmacology 26, 981–986.

Duman, R.S., Heninger, G.R., Nestler, E.J., 1997a. A molecular and cellular theory of depression. Arch. Gen. Psychiatry 54, 597–606.

Duman, R.S., Nibuya, M., Vaidya, V.A., 1997b. A role for CREB in antidepressant activity. In: Skolnick, P. (Ed.), Antidepressants. New Pharmacological Strategies. Humana Press, Totowa, NJ, pp. 172–194.

Dziedzicka-Wasylewska, M., Rogoz, R., Klimek, V., Maj, J., 1997. Repeated administration of antidepressant drugs affects the levels of mRNA coding for D_1 and D_2 dopamine receptors in the rat brain. J. Neural Transm. 104, 515–524.

Eiring, A., Manier, D.H., Bieck, P.R., Howells, R.D., Sulser, F., 1992. The 'serotonin/norepinephrine link' beyond the beta adrenoceptor. Mol. Brain Res. 16, 211–214.

Enna, S.J., Karbon, E.W., 1987. Receptor regulation; evidence for a relationship between phospholipid metabolism and neurotransmitter receptor-mediated cAMP formation in brain. Trends Pharm. Sci. 8, 21–24.

Fleischman, A., Prolov, K., Abarbanel, J., Belmaker, R.H., 1995. The effect of transcranial magnetic stimulation of rat brain on behavioral models of depression. Brain Research 699, 130–132.

Frechilla, D., Otano, A., Del Rio, J., 1998. Effect of chronic antidepressant treatment on transcription factor binding activity in rat hippocampus and frontal cortex. Prog. Neuropsychopharmacol. Biol. Psychiatry 22, 787–802.

Fuller, R.W., Perry, K.W., Molloy, B.B., 1974. Effect of an uptake inhibitor on serotonin metabolism in rat brain: studies with 3-(*p*-trifluoromethylphenoxy)-*N*-methyl-3-phenylpropylamine (Lilly 110140). Life Sci. 15, 1161–1171.

George, M.S., Wassermann, E.M., Kimbrell, T.A., Little, J.T., Williams, W.E., Danielson, A.L., Greenberg, B.D., Hallett, M., Post, R.M., 1997. Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo-controlled crossover trial. Am. J. Psychiatry 154, 1752–1756.

George, M.S., Wassermann, E.M., Williams, W.A., Callahan, A., Ketter, T.A., Basser, P., Hallett, M., Post, R.M., 1995. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. NeuroReport 14, 1853–1856.

Harkin, A.J., Bruce, K.H., Craft, B., Paul, I.A., 1999. Nitric oxide synthase inhibitors have antidepressant-like properties in mice: 1. Acute treatments are active in forced swim test. Eur. J. Pharmacol. 372, 207–213.

Harkin, A., Nowak, G., Paul, I.A., 2000. Noradrenergic lesion antagonizes desipramine-induced adaptation of NMDA receptors. Eur. J. Pharmacol. 389, 187–192.

Heilig, M., Wahlestedt, C., Ekman, R., Widerlov, E., 1988. Antidepressant drugs increase the concentration of neuropeptide Y (NPY)-like immunoreactivity in the rat brain. Eur. J. Pharmacol. 147, 465–467.

Holsboer, F., Spengler, D., Heuser, I., 1992. The Role of Corticotropin-Releasing Hormone in the Pathogenesis of Cushing's Disease, Anorexia Nervosa, Alcholism, Affective Disorders and Dementia. In: Swaab, D.F., Hofman, M.A, Mirmiran, M., Ravid, R., van Leeuwen, F.W. (Eds.), Prog. Brain Res. vol. 93 Elsevier Science Publishers, pp. 385–417.

Houslay, M.D., 1991. "Crosstalk" a pivotal role for protein kinase C in modulating relationships between signal transduction pathways. Eur. J. Biochem. 195, 9–27.

Huang, N.-Y., Layer, R.T., Skolnick, P., 1997. Is an adaptation of NMDA receptors an obligatory step in antidepressant action? In: Skolnick, P. (Ed.), Antidepressants. New Pharmacological Strategies. Humana Press, Totowa, NJ, pp. 125–143.

Hyttel, J., 1977. Neurochemical characterization of a new potent and selective serotonin uptake inhibitor: Lu 10-171. Psychopharmacology (Berlin) 51, 225–233.

Jakobs, K.H., Watanabe, Y., Bauer, S., 1986. Interactions between the hormone-sensitive cyclase system and the phosphoinositide-metabolizing pathway in human platelets. J. Cardiovasc. Pharmacol. 8, S61–S64.

Janowsky, A., Okada, F., Manier, D.H., Applegate, C.D., Sulser, F., Steranka, L.R., 1982. Role of serotonergic input in the regulation of the beta adrenergic receptor coupled adenylate cyclase system. Science 218, 900–901.

Kapur, S., Mann, J.J., 1992. Role of the dopaminergic system in depression. Biol. Psychiatry 32, 1–17.

Karbon, E.W., Shenolikar, S., Enna, S.J., 1986. Phorbol esters enhance a neurotransmitter-stimulated cyclic AMP production in rat brain slices. J. Neurochem. 47, 1566–1575.

Katada, T., Gilman, A.G., Watanabe, Y., Bauer, S., Jakobs, K.H., 1985. Protein kinase C phosphorylates the inhibitory guanine-nucleotide-binding regulatory component and apparently suppresses its function in hormonal inhibition of adenylate cyclase. Eur. J. Biochem. 151, 431–437.

Kiefer, G., Fischer, W., Feuerstein, T.J., 1999. Effects of amitriptyline, amitriptylinoxide, doxepine and clozapine on *N*-methyl-D-aspartate-evoked release of [^{3}H]-acetylcholine in rat caudatoputamen. Arzneimittelforschung 49, 820–823.

Koe, B.K., Weissman, A., Welch, W.M., Browne, R.G., 1983. Sertraline, 1S,4S-*N*-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthylamine, a new uptake inhibitor with selectivity for serotonin. J. Pharmacol. Exp. Ther. 226, 686–700.

Koob, G.F., 1996. Hedonic valence, dopamine and motivation. Mol. Psychiatry 1, 186–189.

Kramer, M.S., Cutler, N., Feighner, J., Shrivastava, R., Carman, J., Sramek, J.J., Reines, S.A., Liu, G., Snavely, D., Wyatt-Knowles, E., Hale, J.J., Mills, S.G., MacCoss, M., Swain, C.J., Harrison, T., Hill, R.G., Hefti, F., Scolnick, E.M., Cascieri, M.A., Chicchi, G.G., Sadowski, S., Williams, A.R., Hewson, L., Smith, D., Carlson, D.J., Hargreaves, R.J., Rupniak, N.M., 1998. Distinct mechanism for antidepressant activity by blockade of central substance P receptors. Science 281, 1640–1645.

Layer, R.T., Popik, P., Olds, T., Skolnick, P., 1995. Antidepressant-like actions of the polyamine site NMDA antagonist, eliprodil. Pharmacol. Biochem. Behav. 52, 621–627.

Leeb-Lundberg, L.M.F., Cotecchia, S., Lomasney, J.W., DeBernardis, J.F., Lefkowitz, R.J., Caron, M.G., 1985. Phorbol esters promote α_1-adrenergic receptor phosphorylation and receptor uncoupling from inositol phospholipid metabolism. Proc. Natl. Acad. Sci. U.S.A. 82, 5651–5655.

Lehmann, H.E., Ban, T.A., Schwartz, G.V., 1975. Psychotherapeutic profile of a new psychoactive drug trazodone (AF-1161). Int. Pharmacopsychiatry 10, 42–53.

Lesch, K.P., Manji, H.K., 1992. Signal transducing G proteins and antidepressant drugs: evidence for modulation of alpha subunit gene expression in rat brain. Biol. Psychiatry 32, 549–579.

Lindsay, R.M., Wiegand, S.J., Anthony Altar, C.A., DiStefano, P.S., 1994. Neurotrophic factors: from molecule to man. Trends Neurosci. 17, 182–190.

Maj, J., 1984. Central effects following repeated treatment with antidepressant drugs. Pol. J. Pharmacol. Pharm. 36, 87–99.

Maj, J., Dziedzicka-Wasylewska, M., Rogoż, R., Rogóż, Z., Skuza, G., 1996. Antidepressant drugs given repeatedly change the binding of the dopamine D_2 receptor agonist [^{3}H]N-0437 to dopamine D_2 receptors in the rat brain. Eur. J. Pharmacol. 304, 49–54.

Maj, J., Dziedzicka-Wasylewska, M., Rogoz, R., Rogóz, Z., 1998. Effect of antidepressant drugs administered repeatedly on the dopamine D_3 receptors in the rat brain. Eur. J. Pharmacol. 351, 31–37.

Maj, J., Papp, M., Skuza, G., Bigajska, K., Zazula, M., 1989a. The influence of repeated treatment with imipramine, (+)- and (−)-oxaprotiline on behavioural effects of dopamine D-1 and D-2 agonists. J. Neural Transm. 76, 29–38.

Maj, J., Rogoz, Z., Skuza, G., 1992. The effects of combined treatment with MK-801 and antidepressant drugs in the forced swimming test in rats. Pol. J. Pharmacol. Pharm. 44, 217–226.

Maj, J., Rogóż, Z., Skuza, G., Sowińska, H., 1984. Repeated treatment with antidepressant drugs potentiates the locomotor response to (+)-amphetamine. J. Pharm Pharmacol. 36, 127–130.

Maj, J., Rogóż, Z., Skuza, G., Sowińska, H., 1989b. Antidepressants given repeatedly increase the behavioural effect of dopamine D-2 agonist. J. Neural Transm., Gen., Sect. 78, 1–8.

Maj, J., Wedzony, K., Klimek, V., 1987. Desipramine given repeatedly enhances behavioural effects of dopamine and d-amphetamine injected into the nucleus accumbens. Eur. J. Pharmacol. 140, 179–185.

Manier, D.H., Eiring, A., Shelton, R.C., Sulser, F., 1996. Beta-adrenoceptor-linked protein kinase A (PKA) activity in human fibroblasts from normal subjects and from patients with major depression. Neuropsychopharmacology 15, 555–561.

Manji, H.K., Lenox, R.H., 1999. Protein kinase C signaling in the brain: molecular transduction of mood stabilization in the treatment of manic-depressive illness. Biol. Psychiatry 46, 1328–1351.

Mann, J.J., Friedman, E., Georgotas, A., Gershon, S., 1980. The antidepressant effects of trazodone and inhibition of platelet serotonin reuptake. Commun. Psychopharmacol. 4, 293–301.

Mansbach, R.S., Brooks, E.N., Chen, Y.L., 1997. Antidepressant-like affects of CP-154,526, a selective CRF1 receptor antagonist. Eur. J. Pharmacol. 323, 21–26.

Mongeau, R., Blier, P., de Montigny, C., 1994. Electrophysiolgical assessment of the implication of α_2-adrenergic heteroceptors on serotonin terminals in the mechanism of action of antidepressant drugs. Critical Issues in the Treatment of Affective Disorders. In: Langer, S.Z., Brunello, N., Mendlewicz, J. (Eds.), Int. Acad. Biomed. Drug Res. vol. 9 Karger, Basel, pp. 98–109.

Mori, S., Zanardi, R., Popoli, M., Garbini, S., Brunello, N., Smeraldi, E., Racagni, G., Perez, J., 1998. cAMP-dependent phosphorylation system after short and long-term administration of moclobemide. J. Psychiatr. Res. 32, 111–115.

Nalepa, I., 1993. The effects of chlorpromazine and haloperidol on second messenger systems related to adrenergic receptors. Pol. J. Pharmacol. 45, 399–412.

Nalepa, I., 1994. The effect of psychotropic drugs on the interaction of protein kinase C with second messenger systems in the rat cerebral cortex. Pol. J. Pharmacol. 46, 1–14.

Nalepa, I., Chalecka-Franaszek, E., Vetulani, J., 1993. The antagonistic effect of separate and consecutive chronic treatment with imipramine and ECS on the regulation of α_1-adrenoceptor activity by protein kinase C. Pol. J. Pharmacol. 45, 521–532.

Nalepa, I., Chalecka-Franaszek, E., Vetulani, J., 1996. Modulation by mianserin pretreatment of the chronic electroconvulsive shock effects on the adrenergic system in the cerebral cortex of the rat. Human Psychopharmacol. Clin. Exp. 11, 273–282.

Nalepa, I., Manier, H.D., Gillespie, D.D., Rossby, S.P., Schmidt, D.E., Sulser, F., 1998. Lack of β-adrenoceptor desensitization in brain following the dual noradrenaline and serotonin reuptake inhibitor venlafaxine. Eur. Neuropsychopharmacol. 8, 227–232.

Nalepa, I., Vetulani, J., 1990. Beta down-regulation induced by repeated vasopressin treatment. Eur. J. Pharmacol. 178, 375–376.

Nalepa, I., Vetulani, J., 1991a. Involvement of protein kinase C in the mechanisms of in vitro effects of imipramine on generation of second messengers by noradrenaline in the cerebral cortical slices of the rat. Neuroscience 44, 585–590.

Nalepa, I., Vetulani, J., 1991b. Different mechanisms of β-adrenoceptor downregulation by chronic imipramine and electroconvulsive treatment: possible role for protein kinase C. J. Neurochem. 57, 904–910.

Nalepa, I., Vetulani, J., 1993a. The effect of calcium channel blockade on the action of chronic ECT and imipramine on responses of α_1-and β-adrenoceptors in the rat cerebral cortex. Pol. J. Pharm. 45, 201–205.

Nalepa, I., Vetulani, J., 1993b. Enhancement of the responsiveness of cortical adrenergic receptors by chronic administration of the 5-hydroxytryptamine uptake inhibitor citalopram. J. Neurochem. 60, 2029–2035.

Nalepa, I., Vetulani, J., 1994. The responsiveness of cerebral cortical adrenergic receptors after chronic administration of atypical antidepressant mianserin. J. Psychiatry Neurosci. 19, 120–128.

Nalepa, I., Vetulani, J., 1996. Modulation of electroconvulsive treatment induced β-adrenergic down-regulation by previous chronic imipramine administration: the involvement of protein kinase C. Pol. J. Pharm. 48, 489–494.

Nibuya, M., Moronobu, S., Duman, R.S., 1995. Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. J. Neurosci. 15, 7539–7547.

Nibuya, M., Nestler, E.J., Duman, R.S., 1996. Chronic antidepressant administration increases the expression of cAMP response element binding protein (CREB) in rat hippocampus. J. Neurosci. 16, 2365–2372.

Nowak, G., Kata, M., Jopek, R., Siedlecki, A., 1997. Chronic electroconvulsive treatment increases the activity of nitric oxide synthase in the rat brain. Pol. J. Pharmacol. 49, 379–382.

Nowak, G., Paul, I.A., Popik, P., Young, A., Skolnick, P., 1993. Ca^{2+} antagonists effect an antidepressant-like adaptation of the NMDA receptor complex. Eur. J. Pharmacol. 247, 101–102.

Nowak, G., Redmond, A., McNamara, M., Paul, I.A., 1995. Swim stress increases the potency of glycine at the *N*-methyl-D-aspartate receptor complex. J. Neurochem. 64, 925–927.

Ogren, S.O., Ross, S.B., Hall, H., Holm, A.C., Renyi, A.L., 1981. The pharmacology of zimelidine: a 5-HT selective reuptake inhibitor. Acta Psychiatr. Scand., Suppl. 290, 127–151.

Oswald, I., Brezinova, V., Dunleavy, D.L.F., 1973. On the slowness of action of tricyclic antidepressant drugs. Br. J. Psychiatry 120, 673–677.

Papp, M., Moryl, E., 1994. Antidepressant activity of non-competitive and competitive NMDA receptor antagonists in a chronic mild stress model of depression. Eur. .J Pharmacol. 263, 1–7.

Pascual-Leone, A., Rubio, B., Pallardó, F., Catalá, M.D., 1996. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. Lancet 348, 233–237.

Paul, I.A., Nowak, G., Layer, R.T., Popik, P., Skolnick, P., 1994. Adaptation of the N methyl D aspartate receptor complex following chronic antidepressant treatments. J. Pharmacol. Exp. Ther. 269, 95–102.

Paul, I.A., Trullas, R., Skolnick, P., Nowak, G., 1992. Down-regulation of cortical beta-adrenoceptors by chronic treatment with functional NMDA antagonists. Psychopharmacology (Berlin) 106, 285–287.

Peiffer, A., Veilleux, S., Barden, N., 1991. Antidepressant and other centrally acting drugs regulate glucocorticoid receptor messenger RNA levels in rat brain. Psychoneuroendocrinology 16, 505–515.

Pekary, A.E., Sattin, A., Lloyd, R.L., 1999. Electroconvulsive seizures increase levels of (EEP) in rat brain. Peptides 20, 107–119.

Pepin, M.C., Govindan, M.V., Barden, N., 1992a. Increased glucocorticoid receptor gene promoter activity after antidepressant treatment. Mol. Pharmacol. 41, 1016–1022.

Pepin, M.C., Pothier, F., Barden, N., 1992b. Antidepressant drug action in a transgenic mouse model of the endocrine changes seen in depression. Mol. Pharmacol. 42, 991–995.

Perez, J., Mori, S., Caivano, M., Popoli, M., Zanardi, R., Smeraldi, E., Racagni, G., 1995. Effects of fluvoxamine on the protein phosphorylation system associated with rat neuronal microtubules. Eur. Neuropsychopharmacol. 5, 65–69.

Perez, J., Tinelli, D., Bianchi, E., Brunello, N., Racagni, G., 1991. cAMP binding proteins in the rat cerebral cortex after administration of selective 5-HT and NE reuptake blockers with antidepressant activity. Neuropsychopharmacology 4, 57–64.

Pilc, A., Branski, P., Palucha, A., Aronowski, J., 1999. The effect of prolonged imipramine and electroconvulsive shock treatment on calcium/calmodulin-dependent protein kinase II in the hippocampus of rat brain. Neuropharmacology 38, 597–603.

Pilc, A., Vetulani, J., 1982. Depression by chronic electroconvulsive treatment of clonidine hypotherma and [^{3}H]clonidine binding to rat cortical membranes. Eur. J. Pharmacol. 80, 109–113.

Popik, P., Vetulani, J., 1993. Similar action of imipramine and arginine-vasopressin in the social interaction test. Pol. J. Pharmacol. 45, 323–325.

Popoli, M., Brunello, N., Perez, J., Racagni, G., 2000. Second messenger-regulated protein kinases in the brain: their functional role and the action of antidepressant drugs. J. Neurochem. 74, 21–33.

Popoli, M., Vocaturo, C., Perez, J., Smeraldi, E., Racagni, G., 1995. Presynaptic Ca^{2+}/calmodulin-dependent protein kinase II: autophosphorylation and activity increase in the hippocampus after long-term blockade of serotonin reuptake. Mol. Pharmacol. 48, 623–629.

Pryor, J.C., Sulser, F., 1991. Evolution of monoamine hypotheses of depression. In: Horton, R.W., Katona, C. (Eds.), Biological Aspects of Affective Disorders. Academic Press, London, pp. 77–94.

Przegalinski, E., Budziszewska, B., 1993. The effect of long-term treatment with antidepressant drugs on the hippocampal mineralocorticoid and glucocorticoid receptors in rats. Neurosci. Lett. 161, 215–218.

Randrup, A., Munkvad, I., Fog, R., Gerlach, J., Molander, R., Kjellenberg, B., Scheel-Krueger, J., 1975. Mania, depression and brain dopamine. Curr. Dev. Psychopharmacol. 2, 207–229.

Redei, E., Organ, M., Hart, S., 1999. Antidepressant-like properties of prepro-TRH 178-199: acute effects in the forced swim test. NeuroReport 10, 3273–3276.

Reiach, J.S., Li, P.P., Warsh, J.J., Kish, S.J., Young, L.T., 1999. Reduced adenylyl cyclase immunolabeling and activity in postmortem temporal cortex of depressed suicide victims. J. Affect. Disord. 56, 141–151.

Rogoz, R., Dziedzicka-Wasylewska, M., 1999. Effects of antidepressant drugs on the dopamine D_2/D_3 receptors in the rat brain differentiated by agonist and antagonist binding — an autoradiographic analysis. Naunyn-Schmiedeberg's Arch. Pharmacol. 359, 178–186.

Romero, L., Casanovas, J.M., Hervas, I., Cortés, R., Artigas, F., 1997. Strategies to optimize the antidepressant action of selective serotonin reuptake inhibitors. In: Skolnick, P. (Ed.), Antidepressants. New Pharmacological Strategies. Humana Press, Totowa, NJ, pp. 1–33.

Ross, S.B., Ogren, S.O., Renyi, A.L., 1976. (*Z*)-dimethylamino-1-(4-bromophenyl)-1-(3-pyridyl) propene (h 102/09), a new selective inhibitor of the neuronal 5-hydroxytryptamine uptake. Acta Pharmacol. Toxicol. (Copenhagen) 39, 152–166.

Rossby, S.P., Manier, D.H., Liang, S., Nalepa, I., Sulser, F., 1999. Pharmacological actions of the antidepressant venlafaxine beyond aminergic receptors. Int. J. Neuropsychopharmacol. 2, 1–8.

Rossby, S.P., Perrin, C., Burt, A.M., Nalepa, I., Schmidt, D.E., Sulser, F., 1996. Fluoxetine increases steady-state levels of preproenkephalin mRNA in rat amygdala by a serotonin dependent mechanism. J. Serotonin Res. 3, 69–74.

Rossby, S.P., Nalepa, I., Huang, M., Perrin, C., Burt, A.M., Schmidt, D.E., Gillespie, D.D., Sulser, F., 1995. Norepinephrine-independent regulation of GRII mRNA in vivo by a tricyclic antidepressant. Brain Res. 687, 79–82.

Rossby, S.P., Sulser, F., 1997. Antidepressants: beyond the synapse. In: Skolnick, P. (Ed.), Antidepressants. New Pharmacological Strategies. Humana Press, Totowa, NJ, pp. 195–212.

Sattin, A., 1999. The role of TRH and related peptides in the mechanism of action of ECT. J. ECT 15, 76–92.

Schildkraut, J.J., 1965. The catecholamine hypothesis of affective disorders: a review of supporting evidence. Am. J. Psychiatry 122, 509–522.

Schwaninger, M., Schofl, C., Blume, R., Rossig, L., Knepel, W., 1995. Inhibition by antidepressant drugs of cyclic AMP response element binding protein/cyclic AMP response element directed gene transcription. Mol. Pharmacol. 47, 1112–1128.

Scott, L.V., Dinan, T.G., 1998. Vasopressin and the regulation of hypothalamic–pituitary–adrenal axis function: implications for the pathophysiology of depression. Life Sci. 62, 1985–1998.

Shelton, R.C., Manier, D.H., Peterson, C.S., Ellis, T.C., Sulser, F., 1999. Cyclic AMP-dependent protein kinase in subtypes of major depression and normal volunteers. Int. J. Neuropsychopharmacol. 2, 187–192.

Shelton, R.C., Mainer, D.H., Sulser, F., 1996. cAMP-dependent protein kinase activity in major depression. Am. J. Psychiatry 153, 1037–1042.

Shih, M., Malbon, C.C., 1994. Oligodeoxynucleotides antisense to mRNA encoding protein kinase A, protein kinase C and β-adrenergic receptor kinase reveal distinctive cell-type specific roles in agonist-induced desensitization. Proc. Natl. Acad. Sci. U.S.A. 91, 12193–12197.

Shirayama, Y., Mitsushio, H., Takashima, M., Ichikawa, H., Takahashi, K., 1996. Reduction of substance P after chronic antidepressants treatment in the striatum, substantia nigra and amygdala of the rat. Brain Res.739, 70–78.

Shopsin, B., 1980. Second generation antidepressants. J. Clin. Psychiatry 41, 45–56.

Skolnick, P., 1999. Antidepressants for the new millenium. Eur J Pharmacol 375, 31–40.

Skolnick, P., Layer, R.T., Popik, P., Nowak, G., Paul, I.A., Trullas, R., 1996. Adaptation of *N*-methyl-D-aspartate (NMDA) receptors following antidepressant treatment: implications for the pharmacotherapy of depression. Pharmacopsychiatry 29, 23–26.

Smith, D.W., Hewson, L., Fuller, P., Williams, A.R., Wheeldon, A., Rupniak, N.M., 1999. The substance P antagonist L-760,735 inhibits stress-induced NK(1) receptor internalisation in the basolateral amygdala. Brain Res. 848, 90–95.

Stogner, K.A., Holmes, P.V., 2000. Neuropeptide-Y exerts antidepressant-like effects in the forced swim test in rats. Eur. J. Pharmacol. 387, R9–R10.

Sugden, D., Klein, D.C., 1988. Activators of protein kinase C act at a postreceptor site to amplify cyclic AMP production in rat pinealocytes. J. Neurochem. 50, 149–155.

Sulser, F., Dingell, J.V., 1968. Adrenergic mechanisms in the central action of tricyclic antidepressants and substituted phenothiazines. Agressologie 9, 281–287.

Sulser, F., Vetulani, J., Mobley, P.L., 1978. Mode of action of antidepressant drugs. Biochem. Pharmacol. 27, 257–261.

Tanaka, C., Saito, N., 1992. Localization of subspecies of protein kinase C in the mammalian central nervous system. Neurochem. Int. 21, 499–512.

Trullas, R., Skolnick, P., 1990. Functional antagonists at the NMDA receptor complex exhibit antidepressant actions. Eur J Pharmacol 185, 1–10.

Uvnas-Moberg, K., Bjokstrand, E., Hillegaart, V., Ahlenius, S., 1999. Oxytocin as a possible mediator of SSRI-induced antidepressant effects. Psychopharmacology (Berlin) 142, 95–101.

Vetulani, J., 1984. Complex action of antidepressant treatment on central adrenergic system: possible relevance to clinical effects. Pharmacopsychiatry 17, 16–21.

Vetulani, J., 1997. Current concepts of mechanisms of action of antidepressant treatments based on preclinical studies. Basic and Clinical Science of Mental and Addictive Disorders. In: Judd, L.O., Saletu, B., Filip, V. (Eds.), Bibl. Psychiatr. Karger, Basel, pp. 162–167.

Vetulani, J., Sulser, F., 1975. Action of various antidepressant treatment reduces reactivity of noradrenergic cyclic AMP generating system in limbic forebrain. Nature 257, 495–496.

Vetulani, J., Antkiewicz-Michaluk, L., Rokosz-Pelc, A., Pilc, A., 1983. Chronic electroconvulsive treatment enhances the density of [^{3}H]prazosin binding sites in the central nervous system of the rat. Brain Res. 275, 392–395.

Vetulani, J., Antkiewicz-Michaluk, L., Rokosz-Pelc, A., 1984. Chronic administration of antidepressant drugs increases the density of cortical ^{3}H prazosin binding sites in the rat. Brain Res. 310, 360–362.

Vetulani, J., Stawarz, R.J., Dingell, J.V., Sulser, F., 1976. A possible common mechanism of action of antidepressant treatments. Reduction in the sensitivity of the noradrenergic cyclic AMP generating system in the rat limbic forebrain. Naunyn-Schmiedeberg's Arch. Pharmacol. 293, 109–114.

Vetulani, J., Stawarz, R.J., Sulser, F., 1975. Adaptive mechanisms in the norepinephrine-sensitive cyclic AMP generating system in the slices of the rat limbic forebrain. Fed. Proc. 34, 266.

Wachtel, H., 1989. Dysbalance of neuronal second messenger function in the aetiology of affective disorders: a pathophysiological concept hypothesising defects beyond first messenger receptors. J. Neural Transm. 75, 21–29.

Wahlestedt, C., Blendy, J.A., Kellar, K.J., Heilig, M., Widerlov, E., Ekman, R., 1990. Electroconvulsive shocks increase the concentration of neocortical and hippocampal neuropeptide Y (NPY)-like immunoreactivity in the rat. Brain Res. 507, 65–68.

Wahlestedt, C., Hakanson, R., 1986. Effects of neuropeptide Y (NPY) at the sympathetic neuroeffector junction. Can pre- and postjunctional receptors be distinguished? Med. Biol. 64, 85–88.

Wahlestedt, C., Skagerberg, G., Ekman, R., Heilig, M., Sundler, F., Hakanson, R., 1987. Neuropeptide Y (NPY) in the area of the hypothalamic paraventricular nucleus activates the pituitary–adrenocortical axis in the rat. Brain Res. 417, 33–38.

Wang, J.F., Asghari, V., Rockel, C., Young, L.T., 1999. Cyclic AMP responsive element binding protein phosphorylation and DNA binding is decreased by chronic lithium but not valproate treatment of SH-SY5Y neuroblastoma cells. Neuroscience 91, 771–776.

Watkins, C.J., Pei, Q., Newberry, N.R., 1998. Differential effects of electroconvulsive shock on the glutamate receptor mRNAs for NR2A, NR2B and mGluR5b. Brain Res. Mol. Brain Res. 61, 108–113.

Wedzony, K., Klimek, V., Nowak, G., 1995. Rapid down-regulation of beta-adrenergic receptors evoked by combined forced swimming test and CGP 37849–a competitive antagonist of NMDA receptors. Pol. J. Pharmacol. 47, 537–540.

Widerlov, E., Lindstrom, L.H., Wahlestedt, C., Ekman, R., 1988. Neuropeptide Y and peptide YY as possible cerebrospinal fluid markers for major depression and schizophrenia, respectively. J. Psychiatr. Res. 22, 69–79.

Wielosz, M., 1981. Increased sensitivity to dopaminergic agonists after repeated electroconvulsive shock (ECS) in rats. Neuropharmacology 10, 941–945.

Willner, P., 1997. The mesolimbic dopamine system as a target for rapid antidepressant action. Int. Clin. Psychopharmacol. Suppl. 3, S7–S14.

Yoshikawa, K., Sabol, S.L., 1986. Expression of the enkephalin precursor gene in C6 rat glioma cells: regulation by beta-adrenergic agonists and glucocorticoids. Brain Res. 387, 75–83.

Yuan, P., Chen, G., Manji, H.K., 1999. Lithium activates the c-Jun NH2-terminal kinases in vitro and in the CNS in vivo. J. Neurochem. 73, 2299–2309.

Zanardi, R., Artigas, F., Franchini, L., Sforzini, L., Gasperini, M., Smeraldi, E., Perez, J., 1997. How long should pindolol be associated with paroxetine to improve the antidepressant response? J. Clin. Psychopharmacol. 17, 446–450.

Zyss, T., 1994. Deep magnetic brain stimulation — the end of psychiatric electroshock therapy? Med. Hypotheses 43, 69–74.

Zyss, T., Górka, Z., Kowalska, M., Vetulani, J., 1997. Preliminary comparison of behavioral and biochemical effects of chronic transcranial magnetic stimulation and electroconvulsive shock in the rat. Biol. Psychiatry 42, 920–924.